Unusual cognitive and behavioural profile in a Williams syndrome patient with atypical 7q11.23 deletion

C Gagliardi, M C Bonaglia, A Selicorni, R Borgatti, R Giorda

J Med Genet 2003;**40**:526–530

Williams syndrome (WS, MIM 194050) is a rare (frequency 1/20 000) multisystemic disorder[1] caused by haploinsufficiency of genes at 7q11.23.[2–4] WS is associated with dysmorphic facial features, supravalvular aortic stenosis (SVAS) and other cardiovascular diseases, infantile hypercalcaemia, and growth deficiency. The full intelligence quotient (IQ) of WS subjects is usually in the 50s to 60s, with a unique cognitive profile, characterised by relatively good verbal abilities alongside a low level of spatial and constructive organisation.[5–7] This different pattern of abilities has been named the "WS cognitive profile" (WSCP).[8]

More than 95% of clinically defined WS patients have a de novo deletion of about 1.5 Mb, with the breakpoints clustered within two highly homologous regions flanking the WS region.[9] Several genes have been mapped within the deleted region,[10] including syntaxin 1A (*STX1A*)[11] that codes for a component of the synaptic apparatus, and *RFC2*[12] that encodes a subunit of the replication factor C complex.

While *ELN* haploinsufficiency has been associated with the cardiovascular and possibly connective tissue abnormalities of WS,[13] the role of other genes in the remaining clinical features of the disease is not known. In particular, it is not clear which gene(s) is responsible for the cognitive and personality profile characteristic of WS patients. It has been reported[8] that patients with deletions of only *ELN* and *LIMK1* show the characteristic WSCP, generally without mental retardation, but analysis of additional patients harbouring small deletions involving *ELN* and *LIMK1*[14] did not confirm these results. *Limk1* deficient mice exhibit significant abnormalities in spine morphology and synaptic function. They also show altered spatial learning and fear response.[15] The *CYLN2* gene, coding for the cytoplasmic linker protein CLIP-115,[16] localised in the dendritic lamellar bodies of neurones and cerebellar glia cells,[17] has also been considered a good candidate. Very recently, targeted mutation of *Cyln2* has produced evidence that in the mouse haploinsufficiency of the gene produces brain abnormalities, hippocampal dysfunction, and particular deficits in motor coordination.[18]

We have identified a patient with many clinical features of WS and a peculiar cognitive profile, without specific spatial and constructive impairment, carrying a 7q11.23 deletion with an atypical telomeric breakpoint.

Key points

- We have identified a patient with a smaller deletion in the WS critical region and an atypical cognitive and behavioural profile.
- The patient had SVAS and vesicoureteric reflux with megaureter. He had normal development, with a mild delay in language acquisition.
- The subject's cognitive performance was compared to an age matched control group of nine WS subjects with a typical deletion (WSCG) and the results were significantly different for both general intelligence (borderline IQ *v* mild impairment) and for visuospatial and visuoconstructive abilities (relatively preserved *v* compromised). His cognitive profile did not show the usual WS cognitive and behavioural pattern. His development differs from both the WSCG and normally developing children.
- The patient's deletion ranges from the centromeric common breakpoint region to beyond marker D7S613 and includes elastin (*ELN*), *LIMK1*, and at least a portion of *CYLN2*.
- Our results suggest that deletion of *CYLN2* may cause cognitive impairment, but is not sufficient to produce the typical WSCP. The *GTF2I* gene located in the telomeric portion of the WS critical region could be responsible for some of the cognitive and behavioural features of the disease.

MATERIALS AND METHODS

Cytogenetic investigations

Chromosome analysis was performed on the proband's blood using standard high resolution techniques. Fluorescent in situ hybridisation (FISH) with the commercially available probe WSR (Vysis Inc, Downers Grove, IL) was performed on the proband's metaphase spreads. Other FISH experiments were performed with bacterial artificial chromosome (BAC) and prokaryotic artificial chromosome (PAC) clones labelled with biotin-dUTP (Vector Laboratories, Burlingame, CA) using nick translation; the labelled probes were visualised with FITC-avidin (Vector Laboratories) and the chromosomes were counterstained with DAPI (Sigma, Milano, Italy); hybridisations were analysed with a Zeiss Axioplan epifluorescence microscope and images captured with a Power Gene FISH System (PSI, Newcastle Upon Tyne, UK).

DNA analysis

Microsatellite analysis was conducted on peripheral blood DNA extracted by standard techniques following the protocol described in Perez-Jurado *et al*.[9] The portion of intron 1 of the *CYLN2* gene containing the previously unreported 4 bp microsatellite polymorphism was amplified with primers CYLN2 i1F (5'-CTCTTCCCTTTCGGTTGTAAATGT-3', ABI-Fam labelled) and CYLN2 i1R (5'- CGCCTCCACCTGCCTCTTCT-3') and the same PCR protocol used for the other polymorphisms. All primers were purchased from MWG Biotech (Ebersberg, Germany). The 473/477 bp fragments were visualised like all other polymorphisms on an ABI PRISM 310 Genetic Analyzer (Applera, Monza, Italy). The CYLN2 i1 polymorphism was verified in 50 unrelated normal subjects: 36 were 473/473, 13 473/477, and one was 477/477. Allele frequencies were 0.85 for the 473 bp allele and 0.15 for the 477 bp allele. All sequencing reactions were performed with a Big Dye terminator cycle sequencing kit (Applera). Sequences were run on an ABI Prism 310 Genetic Analyzer.

RESULTS

Clinical description

The proband is a 5½ year old boy, the second child of healthy, unrelated parents. Written informed consent for the neuropsychological examination and the genetic analysis was obtained from his parents. The pregnancy was uneventful,

Figure 1 Photograph of the subject aged 5½ years.

except for mild intrauterine growth retardation during the third trimester, shown by ultrasound examination. At birth the child's weight was 2450 g (25th centile), his length was 45 cm (3rd centile), and his head circumference was 34 cm (25th centile). His Apgar scores were 10/10. He had supravalvular aortic stenosis (SVAS, surgically corrected at the age of 23 months) and vesicoureteric reflux with right megaureter (surgically corrected at the age of 17 months). The following facial dysmorphism was evident: mild coarsening of facial features, bitemporal narrowing, sparse eyebrows, downward slanting palpebral fissures, deep set eyes, prominent cheeks, bulbous triangular nasal tip, long and featureless philtrum, and macrostomia (fig 1).

Neurological evaluation was normal, except for slightly decreased muscle tone, with hypertonia of the tibiotarsal joints and increased deep tendon reflexes. Balance was adequate.

Neuropsychological testing

The patient's psychomotor milestones were mildly delayed; he sat at the age of 8 months, walked at 12 months, and spoke his first words at 18 months and first sentences at 36 months. His cognitive profile was assessed at the age of 5½ years. We used a general intelligence test, the Stanford Binet Development Scale,[19] and a neuropsychological battery, VMI block construction[20] and Rey Figure,[21] in order to assess visual-spatial and visuoconstructive abilities; verbal and spatial working memory and recall memory for drawings were assessed respectively by Digit Span, Corsi Span,[22] and Rey Figure Memory task (table 1). The subject showed borderline IQ (IQ=83), with some difficulties in vocabulary (mildly restricted), syntactic organisation (poor), and comprehension. His performance in visual-spatial and visuoconstructive tasks was borderline, like his IQ. Verbal and spatial working memory were mildly impaired, without significant differences between verbal and non-verbal domains. His social behaviour was friendly, and no anxiety trait or overfriendly manner could be detected.

The patient's performance was compared to a group of age matched subjects (six boys and three girls, mean age 5.12 years, SD 0.66) with Williams syndrome and the typical deletion (Williams syndrome Control Group, WSCG), who underwent the same test battery (table 1). The WSCG's performance was characterised by mild cognitive impairment (IQ=68.67, SD 16.29), major impairment in non-verbal abilities, mainly in visuoconstructive tasks, and a very low level of spatial organisation; verbal working memory was better than spatial. The WSCG displayed the typical Williams syndrome cognitive profile. The proband's and WSCG's test performances are compared in the last column of table 1. The difference in IQ was statistically significant. The patient's performance was similar to the WSCG in language tasks, but significantly better in spatial and constructive organisation. In fact the nine children of the WSCG were not able to perform the Rey Figure task (copy and memory), which is sensitive to the ability to organise spatially and hierarchically a graphic performance by first copying from a model and later recalling it, while the proband performed at a level adequate to his mental age.

Similar data were obtained from the second copy and draw test, the VMI test. No significant differences with the WSCG were shown by the other tests (block construction, Digit and Corsi Span).

Genetic analysis

FISH analysis using the commercially available probe WSR (Vysis) showed hemizygosity at the *ELN*, *LIMK1*, and D7S613 loci. FISH with clone CTB-8H17, partially overlapping the centromeric cluster of repeated sequences[23] (BAC 1008H17), detected a partial deletion showing a small signal on one chromosome 7 compared to its homologue (fig 2A). The result was confirmed by performing a FISH analysis on a subject with typical WS deletion; the probe shows the same pattern as observed in our patient (fig 2B), as previously described.[23] Additional FISH experiments with clones RP4-665P5[24] (fig 2C), RP11-815K3, and CTB-139P11[25] gave signals of equal

Table 1 Neuropsychological test scores obtained from the proband, compared to the results obtained from a control group of nine WS subjects with typical deletion. The p value (normal distribution) is shown in the last column; significant p values (p<0.05) are highlighted in bold

Tests	WS subjects with typical deletion		Proband score	p
	Average score	SD		
Chronological age (y)	5.12	0.66	5.60	0.4654
Mental age (y)	3.39	0.63	4.82	**0.0484**
IQ (score)	68.67	16.29	83.00	**0.0166**
Corsi Span (score for years)	3.60		3.60	
Digit Span (score for years)	1.80	2.14	3.00	0.1595
VMI (score for years)	3.30	0.38	4.30	**0.0353**
Rey Figure copy (score for years)	Unmeasurable		4.60	
Rey Figure memory (score for years)	Unmeasurable		4.60	
Blocks - WISC-R (score)	1.40	1.20	2.00	0.2934

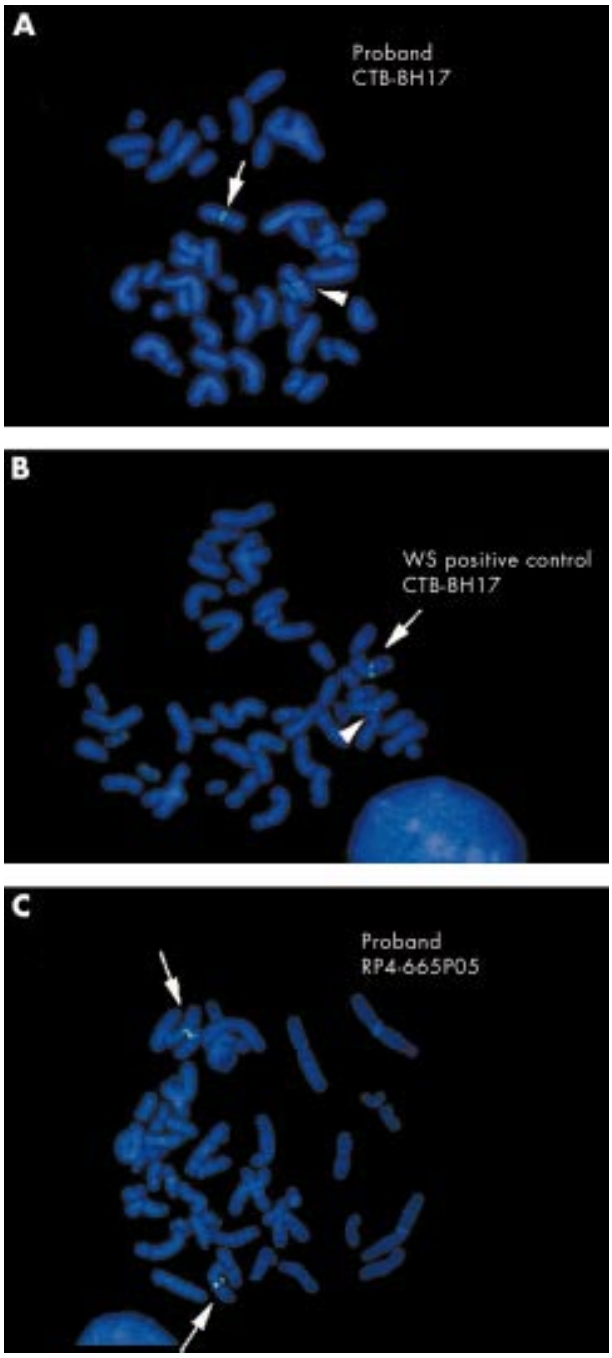

Figure 2 FISH analysis of metaphase chromosomes from the patient (A, C) and from a control subject with a typical WS deletion (B). In the patient (A), FISH with BAC clone CTB-8H17 generates a small signal on one chromosome 7 (arrowhead) compared to the other (arrow), indicating a partial deletion. The same result is obtained analysing a subject with a typical WS deletion (B). The clone CTB-8H17, partially overlapping the centromeric cluster of repeated sequences, gives a partial deletion pattern in subjects with the typical WS deletion, as described previously.[23] FISH with PAC probe RP5-665P05 (C) shows signals of equal intensity on both chromosomes 7 (arrows).

intensity on both chromosome 7 homologues, indicating absence of deletion.

Microsatellite analysis[9] on peripheral blood DNA from the patient, his brother, and his parents confirmed hemizygosity for marker D7S613 and the paternal origin of the deletion, but showed dizygosity for D7S1870. Markers D7S653, D7S1816, D7S489A, and D7S669 were also heterozygous. All other

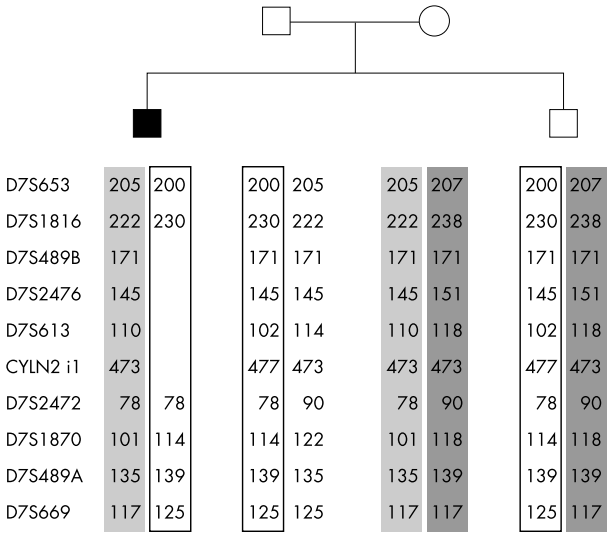

Figure 3 Molecular genotyping of the proband and his family with microsatellite probes in the WS region. The numbers indicate allele size in base pairs. Alleles belonging to the same haplotype have been vertically aligned and shaded. In the proband, markers D7S489B and D7S2476 have been drawn as deleted based on the FISH results with probe CTB-8H17; marker D7S2472 has been drawn as non-deleted because of FISH results with probe RP5-665P05; marker CYLN2 i1 has been considered deleted for the reasons outlined in the results section.

markers were uninformative (fig 3). The proband and his brother inherited different chromosome 7 haplotypes from their mother and the same haplotype from their father. In the proband the deletion was not associated with a recombination.

Typing of a previously undescribed 4 bp (TTCA) insertion/deletion polymorphism in intron 1 of the *CYLN2* gene (1066 bp downstream of exon 1; position 11736822 on sequence NT_007758.8) showed that the proband's deletion includes at least the 5′ end of the gene. In fact, the proband and his brother inherited the same paternal haplotype carrying the 477 bp CYLN2 i1 allele, but the proband only has the 473 bp allele (fig 3). He could have inherited his father's 473 bp allele only in the unlikely event of a double crossover. Sequence analysis of all *RFC2*[12] and *CYLN2*[16] exons and of several intronic single nucleotide polymorphisms (SNPs) in the region (not shown) did not show any other informative polymorphism.

These results map the extent of the deletion from the typical WS breakpoint on the centromeric side to between intron 1 of *CYLN2* and PAC clone RP4-665P5 on the telomeric side (fig 4).

DISCUSSION

The subject described here meets the diagnostic criteria for WS (clinical features, SVAS, short stature, positive FISH analysis), but his clinical and neuropsychological profiles are unusual. Face features are typical for WS, but more mildly expressed; moreover, inspection of photographs taken at different periods through infancy and childhood showed a gradual reduction of WS facial features (data not shown). The cognitive profile displayed by the patient was different in a number of ways from the WSCG. He had borderline IQ, while the age matched WSCG children were mildly impaired. He did not show the usual WS behavioural pattern. Moreover, his cognitive profile did not show the typical spatial and constructive impairment. However, the patient showed impairment in several competencies. In this sense, his development differs from both the WSCG and normally developing children.

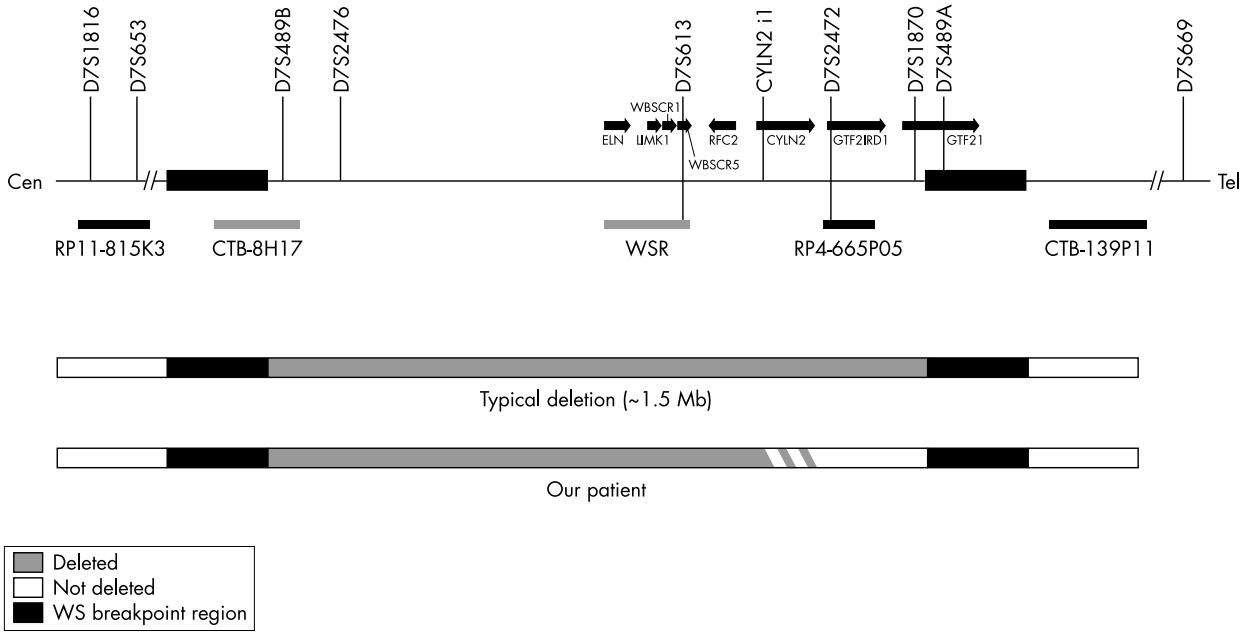

Figure 4 Physical map of the WS region at 7q11.23 (not drawn to scale) showing the relative location of the probes used for FISH analysis (thick horizontal lines), informative polymorphic markers (vertical lines), and selected genes (arrows).

Very few subjects with deletions that do not span the entire WS region have been reported so far.[8 14 23 26–29] Two patients carrying a deletion spanning from *ELN* to marker D7S1870 still had the full WS phenotype.[26] Tassabehji *et al*[14] and Karmiloff-Smith *et al*[28] accurately described a SVAS patient carrying a large deletion encompassing all genes in the WS region with the exception of *CYLN2*, *GTF2IRD1*, and *GTF2I*, but no clinical and cognitive WS phenotype. They used the British Abilities Scale II (BAS) scale for the assessment of cognitive abilities, and showed "an above average, even cognitive profile, with no indication of spatial impairment." Since there is no standardisation of the BAS scale for the Italian population, we used a different cognitive assessment, but explored the same functional areas.

Our patient's profile is different from that of the subject they described because of his borderline cognitive abilities but similar in the absence of the typical spatial constructive impairment. In the subject described by Korenberg *et al*[23] (subject RM1199), all genes between *FZD9* and *WSCR1* were deleted, while *RFC2*, *CYLN2*, *GTF2IRD1*, and *GTF2I* were not. This 8 year old girl had SVAS, some minor dysmorphisms, and mild mental retardation. No information on her cognitive or behavioural profile was available. Del Campo *et al*[29] reported a family with SVAS, borderline mental functioning, gregarious personality, minor facial WBS, and absence of visual/spatial deficits. Molecular analysis showed a 700 kb deletion including all genes from *ELN* to *GTF2IRD1*.

The *GTF2I* gene, located in the telomeric copy of the WS typical breakpoint region and deleted in all WS subjects with a typical deletion,[30] is not deleted in our patient. This gene encodes BAP-135, a protein phosphorylated by Bruton's tyrosine kinase, as well as the transcription factor TFII-I. The centromeric copy of the WS breakpoint region contains a highly similar (99.9% throughout the coding region) transcribed pseudogene, *GTF2IP1*.[30] The *GTF2IRD1* gene, coding for a putative transcription factor with ubiquitous expression,[31 32] may also be preserved. All the other genes in the WS region are deleted.

We cannot rule out that in our patient *CYLN2* may be expressed from an alternative promoter located downstream from the known exon 1, since the transcription pattern of human *CYLN2* has not been fully analysed and its protein coding region starts in exon 2.[16] On the other hand, a deletion involving at least exon 1 and the entire upstream regulatory portion of the gene is likely to have major effects on its expression.

Tassabehji *et al*[14] suggested that all determinants of the WS phenotype, apart from SVAS, lie telomeric to *RFC2*. Our observations indicate that, while the WS phenotype is the result of the haploinsufficiency of a number of genes, the deletion of the *GTF2IRD1* and/or *GTF2I* genes located on the telomeric side of the WS region is necessary for the syndrome's unique cognitive profile. Transgenic mice carrying a disrupted *Gtf2ird1* gene[33] did not show any obvious impairment, although it must be pointed out that they were not tested in detail for subtle cognitive and behavioural defects. It is also interesting to note that Osborne *et al*[24] described a subject with WS facies, developmental delay, and WS-like behavioural profile (subject 12503) carrying an inversion of the WS region, and hypothesised that *GTF2I* may have been affected by the rearrangement. The *GTF2I* gene may then be critical for the WSCP.

Our data also show that hemizygosity for *LIMK1* and *CYLN2*, while not sufficient to generate the WSCP, may cause alterations in the cognitive profile. Very likely, deletion of *GTF2I, GTF2IRD1*, and *CYLN2* (and perhaps *LIMK1*) is necessary to cause the typical WSCP. When, as in the case of our patient, one or more of these genes is preserved, the result is a milder phenotype, with some cognitive impairment (borderline IQ) and a variable loss of visual-spatial and constructive abilities.

Identification of additional subjects with atypical deletions, careful comparison of their genetic, clinical, and neuropsychological profiles, and the development of methods for the molecular analysis of *GTF2I* will be needed in order to assess the contribution of each gene to the WS phenotype.

ACKNOWLEDGEMENTS

The authors wish to thank the family of the patient for their cooperation, Lucy Osborne and Stephen Scherer for their gift of clones CTB-139P11 and RP11-815K3, and Uberto Pozzoli, Maria Teresa Bassi, and Manuela Sironi for their helpful suggestions. This study was supported in part by grant ICS 030.10/RF97.37 from the Italian Ministry of Health

Authors' affiliations
C Gagliardi, M C Bonaglia, R Borgatti, R Giorda, IRCCS "E Medea", Bosisio Parini, Lecco, Italy
A Selicorni, Clinica Pediatrica De Marchi, Milano, Italy

Correspondence to: Dr R Giorda, IRCCS "E. Medea", Via Don Luigi Monza 20, 23842 Bosisio Parini (LC), Italy; rgiorda@bp.lnf.it

REFERENCES

1 **Morris CA**, Demsey SA, Leonard CO, Dilts C, Blackburn BL. The natural history of Williams syndrome: physical characteristics. *J Pediatr* 1988;**113**:318-26
2 **Ewart AK**, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, Stock AD, Leppert M, Keating MT. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat Genet* 1993;**5**:11-16.
3 **Lowery MC**, Morris CA, Ewart A, Brothman LJ, Zhu XL, Leonard CO, Carey JC, Keating M, Brothman AR. Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. *Am J Hum Genet* 1995;**57**:49-53.
4 **Nickerson E**, Greenberg F, Keating M, McCaskill C, Shaffer LG. Deletions in the elastin gene at 7q11.23 occur in ~90% of patients with Williams syndrome. *Am J Hum Genet* 1995;**56**:1156-61.
5 **Udwin O**, Yule W. A cognitive and behavioral phenotype in Williams syndrome. *J Clin Exp Neuropsychol* 1991;**13**:232-44.
6 **Bellugi U**, Wang P, Jernigan TL. Williams syndrome: an unusual neuropsychological profile. In: Broman S, Graffman J, eds. *Atypical cognitive defects in developmental disorders: implications for brain function*. Hillsdale, NJ: Lawrence Erlbaum, 1994:23-56.
7 **Jarrold C**, Baddeley AD, Hewes AK. Verbal and non-verbal abilities in the Williams syndrome phenotype: evidence for diverging developmental trajectories. *J Child Psychol Psychiatry* 1998;**39**:511-23.
8 **Frangiskakis JM**, Ewart AK, Morris CA, Mervis CB, Bertrand J, Robinson BF, Klein BP, Ensing GJ, Everett LA, Green ED, Proschel C, Gutowski NJ, Noble M, Atkinson DL, Odelberg SJ, Keating MT. LIM-kinase 1 hemizygosity implicated in impaired visuospatial constructive cognition. *Cell* 1996;**86**:59-69.
9 **Perez-Jurado LA**, Peoples R, Kaplan P, Hamel B, Francke U. Molecular definition of the chromosome 7 deletion in Williams syndrome and parent-of-origin on growth. *Am J Hum Genet* 1996;**59**:781-92.
10 **Francke U**. Williams-Beuren syndrome: genes and mechanisms. *Hum Mol Genet* 1999;**8**:1947-54.
11 **Osborne LR**, Soder S, Shi XM, Pober B, Costa T, Scherer SW, Tsui LC. Hemizygous deletion of the syntaxin 1A gene in individuals with Williams syndrome. *Am J Hum Genet* 1997;**61**:449-52.
12 **Peoples R**, Perez-Jurado L, Wang YK, Kaplan P, Francke U. The gene for replication factor C subunit 2 (*RFC2*) is within the 7q11.23 Williams syndrome deletion. *Am J Hum Genet* 1996;**58**:1370-3.
13 **Ewart AK**, Morris CA, Ensing GJ, Loker J, Moore C, Leppert M, Keating M. A human vascular disorder, supravalvular aortic stenosis, maps to chromosome 7. *Proc Natl Acad Sci USA* 1993;**90**:3226-30.
14 **Tassabehji M**, Metcalfe K, Karmiloff-Smith A, Carette MJ, Grant J, Dennis N, Reardon W, Splitt M, Read AP, Donnai D. Williams syndrome: use of chromosomal microdeletions as a tool to dissect cognitive and physical phenotypes. *Am J Hum Genet* 1999;**64**:118-25.
15 **Meng Y**, Zhang Y, Tregoubov V, Janus C, Cruz L, Jackson M, Lu WY, MacDonald JF, Wang JY, Falls DL, Jia Z. Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. *Neuron* 2002;**35**:121-33.
16 **Hoogenraad CC**, Eussen BH, Langeveld A, van Haperen R, Winterberg S, Wouters CH, Grosveld F, De Zeeuw CI, Galjart N. The murine *CYLN2* gene: genomic organization, chromosome localization, and comparison to the human gene that is located within the 7q11.23 Williams syndrome critical region. *Genomics* 1998;**53**:348-58.
17 **De Zeeuw CI**, Hoogenraad CC, Goedknegt E, Hertzberg E, Neubauer A, Grosveld F, Galjart N. CLIP-115, a novel brain-specific cytoplasmic linker protein, mediates the localization of dendritic lamellar bodies. *Neuron* 1997;**19**:1187-99.
18 **Hoogenraad CC**, Koekkoek B, Akhmanova A, Krugers H, Dortland B, Miedema M, van Alphen A, Kistler WM, Jaegle M, Koutsourakis M, Van Camp N, Verhoje M, van der Linden A, Kaverina I, Grosveld F, De Zeeuw CI, Galjart N. Targeted mutation of *Cyln2* in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. *Nat Genet* 2002;**32**:116-27.
19 **Bozzo MT**, Mansueto ZG. *Adattamento Italiano della Scala di Intelligenza Stanford-Binet forma L-M, nella Revisione Terman-Merrill* (Italian Version L-M form, III revision). Firenze, Italy: Organizzazioni Speciali, 1993.
20 **Beery KE**, Buktenica NA. *Developmental test of visual motor integration*. Student test booklet. Chicago: Follett Publishing, 1967.
21 **Rey A**. *Reattivo della figura complessa*. Firenze: Organizzazioni Speciali, 1968.
22 **Corsi PM**. *Human memory and the medial temporal region of the brain*. Unpublished PhD thesis, McGill University, Montreal, 1972.
23 **Korenberg JR**, Chen XN, Hirota H, Lai Z, Bellugi U, Burian D, Roe B, Matsuoka R. Genome structure and cognitive map of Williams syndrome. *J Clin Neurosci* 2000;**12**:89-107.
24 **Peoples R**, Franke Y, Wang YK, Perez-Jurado L, Paperna T, Cisco M, Francke U. A physical map, including a BAC/PAC clone contig, of the Williams-Beuren syndrome-deletion region at 7q11.23. *Am J Hum Genet* 2000;**66**:47-68.
25 **Osborne LR**, Li M, Pober B, Chitayat D, Bodurtha J, Mandel A, Costa T, Grebe T, Cox S, Tsui LC, Scherer SW. A 1.5 million-base pair inversion polymorphism in families with Williams-Beuren syndrome. *Nat Genet* 2001;**29**:321-5.
26 **Botta A**, Novelli G, Mari A, Novelli A, Sabani M, Korenberg J, Osborne LR, Digiglio MC, Giannotti A, Dallapiccola B. Detection of an atypical 7q11.23 deletion in Williams syndrome patients which does not include the *STX1A* and *FDZ3* genes. *J Med Genet* 1999;**36**:478-80.
27 **Olson TM**, Michels VV, Urban Z, Csiszar K, Christiano AM, Driscoll DJ, Feldt RH, Boyd CD, Thibodeau SN. A 30 kb deletion within the elastin gene results in familial supravalvular aortic stenosis. *Hum Mol Genet* 1995;**4**:1677-9.
28 **Karmiloff-Smith A**, Grant J, Ewing S, Carette MJ, Metcalfe K, Donnai D, Read AP, Tassabehji M. Using case study comparisons to explore genotype-phenotype correlations in Williams-Beuren syndrome. *J Med Genet* 2003;**40**:136-40.
29 **Del Campo** M, Magano LF, Martinez Iglesias J, Perez Jurado LA. Partial features of Williams-Beuren syndrome in a family with a novel 700 kb 7q11.23 deletion. *10th International Congress of Human Genetics, Vienna 2001*: Abstract C055.
30 **Perez-Jurado LA**, Wang YK, Peoples R, Coloma A, Cruces J, Francke U. A duplicated gene in the breakpoint regions of the 7q11.23 Williams-Beuren syndrome deletion encodes the initiator binding protein TFII-I and BAP-135, a phosphorylation target of BTK. *Hum Mol Genet* 1998;**7**:325-34.
31 **Osborne LR**, Campbell T, Daradich A, Scherer SW, Tsui LC. Identification of a putative transcription factor gene (*WBSCR11*) that is commonly deleted in Williams-Beuren syndrome. *Genomics* 1999;**57**:279-84.
32 **Franke Y**, Peoples RJ, Francke U. Identification of GTF2IRD1, a putative transcription factor within the Williams-Beuren syndrome deletion at 7q11.23. *Cytogenet Cell Genet* 1999;**86**:296-304.
33 **Durkin ME**, Keck-Waggoner CL, Popescu NC, Thorgelrsson SS. Integration of a *c-myc* transgene results in disruption of the mouse *Gtf2ird1* gene, the homologue of the human GTF2IRD1 gene hemizygously deleted in Williams-Beuren syndrome. *Genomics* 2001;**73**:20-7.

High frequency of T9 and *CFTR* mutations in children with idiopathic bronchiectasis

V N Ninis, M O Kýlýnç, M Kandemir, E Daðlý, A Tolun

J Med Genet 2003;**40**:530–535

Obstructive pulmonary disease is an important health problem in all populations, and bronchiectasis of unknown aetiology (idiopathic bronchiectasis, IB) contributes significantly to the disease. The gene responsible for cystic fibrosis (CF), the cystic fibrosis transmembrane regulator (*CFTR*), was shown to have a role in the manifestation of IB, as gene mutations and a significantly high proportion of allele T5 of the polythymidine tract (T_n) in intron 8 (IVS8) have been observed in patients.[1–5] However, the complex genetic basis of the phenotype expression of IB remains largely unknown. *CFTR* mutations alone cannot be held responsible for the disease, as obligate *CFTR* mutation heterozygotes were shown not to have